US Pharmacists' Effect as Team Members on Patient Care

Systematic Review and Meta-Analyses

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Background: One approach postulated to improve the provision of health care is effective utilization of team-based care including pharmacists.

Objective: The objective of this study was to conduct a comprehensive systematic review with focused meta-analyses to examine the effects of pharmacist-provided direct patient care on therapeutic, safety, and humanistic outcomes.

Methods: The following databases were searched from inception to January 2009: NLM PubMed; Ovid/MEDLINE; ABI/INFORM; Health Business Fulltext Elite; Academic Search Complete; International Pharmaceutical Abstracts; PsycINFO; Cochrane Database of Systematic Reviews; National Guideline Clearinghouse; Database of Abstracts of Reviews of Effects; ClinicalTrials.gov; LexisNexis Academic Universe; and Google Scholar. Studies selected included those reporting pharmacist-provided care, comparison groups, and patient-related outcomes. Of these, 56,573 citations were considered. Data were extracted by multidisciplinary study review teams. Variables examined included study characteristics, pharmacists' interventions/services, patient characteristics, and study outcomes. Data for meta-analyses were extracted from randomized controlled trials meeting meta-analysis criteria.

Results: A total of 298 studies were included. Favorable results were found in therapeutic and safety outcomes, and meta-analyses conducted for hemoglobin A1c, LDL cholesterol, blood pressure, and adverse drug events were significant ($P < 0.05$), favoring pharmacists' direct patient care over comparative services. Results for humanistic outcomes were favorable with variability. Medication adherence, patient knowledge, and quality of life-general health meta-analyses were significant ($P < 0.05$), favoring pharmacists' direct patient care.

Conclusions: Pharmacist-provided direct patient care has favorable effects across various patient outcomes, health care settings, and disease states. Incorporating pharmacists as health care team members in direct patient care is a viable solution to help improve US health care.

Key Words: pharmacists, direct patient care, systematic review, meta-analysis

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Team-based direct patient care has been identified as an important approach to meet patient needs and improve health care quality.[1] As evidenced by the growing body of literature depicting direct patient care services provided by pharmacists in specific health care settings, patient populations, and disease states, the role of pharmacists as members of the health care team has expanded beyond conventional medication dispensing in the United States. According to Kaboli et al, pharmacists "work directly with providers and patients to provide services not simply associated with dispensing of drugs," but also with medication and disease management (p. 956).[2] The Institute of Medicine (IOM) recognizes the critical role played by pharmacists in the areas of medication safety and management, as well as the value of pharmacist-physician collaboration in patient care.[3–5] Pharmacists who perform direct patient care services (also known as clinical pharmacists in many settings) are specially trained to monitor medication therapy with the goals of achieving desired therapeutic outcomes and reducing adverse health events.[6] Thus, as members of the health care team, pharmacists may provide beneficial contributions directly related to safe, effective, and optimal medication use.

According to the IOM, "To close the gaps between best practice and usual care … will require the collective expertise of a vast array of doctors, nurses, pharmacists, allied health professionals, social workers, and vested laypersons" (p. 43).[5] To more effectively use the expertise of pharmacists as members of interdisciplinary health care teams, it is necessary to better understand the various roles and contributions of pharmacists to patient care. The volume of pharmacy literature available regarding the effects of pharmacists' interventions/services on patient outcomes necessitates a systematic review to study, synthesize, and elucidate pharmacists' effects across diverse settings, disease states, and populations. Previous systematic reviews have been conducted pertaining to pharmacist-provided patient care and generally report favorable findings; however, these studies were limited in scope to specific patient populations, disease states, and/or health care settings.[2,7–17] To date, a systematic review and meta-analyses have not been conducted that broadly encompass existing evidence regarding pharmacist-provided direct patient care services and interventions in the United States. In addition, it has been proposed that evaluation from a multidimensional perspective, rather than simply focusing on therapeutic outcomes, should be used to enhance understanding of the extensive effect of health care; for example, an assessment which integrates clinical (both therapeutic and safety) and humanistic outcomes.[18] Therefore, the overall objective of this study was to conduct a comprehensive systematic review of evidence examining the effects of pharmacists' direct patient care interventions and services on therapeutic, safety, and humanistic health outcomes in the United States, supplemented with focused meta-analyses.

METHODS

Data Sources and Searches

The methods of this systematic review and meta-analyses were based on the "Cochrane Handbook and Systematic Reviews in Health Care: Meta-analysis in Context."[19,20] A team of medical librarians assisted in conducting a comprehensive literature search for each of the following databases from the start date of the database (noted in parentheses) through January 2009: NLM PubMed (1950); Ovid/MEDLINE (1950); ABI/INFORM (1971); Health Business Fulltext Elite (1922); Academic Search Complete (1887); International Pharmaceutical Abstracts (IPA; 1970); PsycINFO (1890); Cochrane Database of Systematic Reviews (1988); National Guideline Clearinghouse (1997); Database of Abstracts of Reviews of Effects (DARE; 1991); ClinicalTrials.gov (2000); LexisNexis Academic Universe (1789); and Google Scholar (1900). Database-specific search terms were used (Appendix A, online only, available at: http://links.lww.com/MLR/A102). In addition, reference lists of systematic reviews, meta-analyses, and review articles were hand-searched to identify articles that were not captured in the electronic database search.

Study Selection

Duplicate references across databases and references not appropriate to the study were eliminated from the literature search reference lists. The following were considered not appropriate for review in this study: non-US studies, descriptive studies with no comparison group, systematic reviews, meta-analyses, clinical drug trials, commentaries, letters, editorials, books, book chapters, meeting abstracts, case studies, guidelines, online exams, bibliographies, dissertations, lectures, theses, book reviews, and news articles. After eliminating duplications and references not appropriate for the study, the remaining references were divided into 2 groups and submitted for inclusion/exclusion assessment by 2 independent teams of multidisciplinary reviewers (each review team consisted of a pharmacist and an expert in social sciences). A pilot-tested study inclusion screening tool was used for the assessment. To be included in the systematic review, studies were required to meet all of the following criteria: (*a*) evidence of pharmacist involvement in direct patient care (able to discern pharmacist contribution); (*b*) comparison group present; and (*c*) patient-related outcomes reported (outcomes must be therapeutic, safety, or humanistic).

Data Extraction

Included studies were indexed according to each of the health-related outcome areas: therapeutic, safety, and humanistic. Multidisciplinary review teams were charged with extracting data from included studies, and each review team consisted of 2 or 3 members with expertise in the relevant outcome area. More specifically, the studies indexed as humanistic were reviewed by an attorney with a Masters in Public Health, a pharmacist, and a licensed, PhD-level social worker; and the studies indexed as safety were reviewed by a pharmacist and an individual with a PhD in Pharmacy Administration. Because of the volume of studies, those indexed as therapeutic were divided between 2 review teams; 1 team consisted of a pharmacist and a physician, and the other team included a pharmacist and a registered nurse who also has a PhD in clinical nursing research.

Data were extracted from full-text studies by each team member independently using a piloted standardized data extraction form to minimize variability. Extracted data were then compared and any differences between team members were identified and resolved. Extracted data included study characteristics (eg, study design, disease state), pharmacists' interventions/services (eg, medication therapy management, disease state management, medication understanding education), patient characteristics (eg, age, gender, type of health insurance), and study outcomes. Study outcome results were collected using the categories defined as follows:

- Favorable: determined by P value less than 0.05 indicating significant improvement as a result of pharmacist-provided care.
- Not Favorable: determined by P value less than 0.05 indicating significant improvement as a result of nonpharmacist-provided care (generally conventional/usual care).

- Mixed: determined by favorable results on one measurement of a study variable, but not favorable or no effect results on another.
- No Effect: determined by no significant differences between pharmacist-provided care and comparison (indicated by *P* value greater than 0.05).
- Unclear: unable to determine outcome based on data presented.

Furthermore, level of outcomes, also referred to as hierarchy of study outcomes, was assessed.[21,22] The hierarchy of study outcomes, modified from the Agency for Healthcare Research and Quality and a systematic review conducted by Roughead et al, was defined as follows: (*a*) Level 1 (considered the highest level), clinical and quality of life (QoL) outcomes, eg, morbidity, mortality, adverse events; (*b*) Level 2, surrogate outcomes, eg, blood glucose, blood pressure, cholesterol levels; (*c*) Level 3, other measureable variables with an indirect or unestablished connection to the target outcome, eg, medication or disease state knowledge; and (*d*) Level 4, other relevant variables, but not direct outcomes, eg, patient satisfaction, potential adverse events.[21,22] Although outcomes representing more than one level may have been present in an individual study, only the highest outcome level was reported.

Data Synthesis and Analysis

Data were analyzed using SPSS statistical software, version 17.0 (SPSS, Inc, Chicago, IL) by reporting summary statistics (frequencies) for all included studies on study characteristics. Studies were also grouped by outcome area (ie, therapeutic, safety, and humanistic), and summary statistics for each area were calculated. Studies reporting results in more than one outcome area were included in the analysis for each relevant area (for example, a study reporting patient adherence and blood pressure levels was included in both humanistic and therapeutic analyses). Similar to previous studies, Pearson's correlation coefficient was used to evaluate the interrater reliability of each review team.[17]

Meta-Analysis

For the meta-analyses, data were extracted from randomized controlled trials (RCTs) that (1) were randomized at the individual patient level; (2) reported the number of individuals in the intervention group and comparison (control) group; and (3) reported outcomes as means and standard deviations or as proportions. If a study reported a mean but no standard deviation, the study was rereviewed to determine whether some other data (eg, confidence intervals) were reported that could be used in the analysis. Within each outcome area (therapeutic, safety, humanistic), meta-analyses were conducted for select outcomes (eg, hemoglobin A1c) for which there were at least 4 studies reporting on the same select outcome.

Data were entered into the Comprehensive Meta-analysis Program (Biostat, Inc, Englewood, NJ). Forest plots were constructed using a random effects model that weighted studies based on sample size, and addressed heterogeneity by assuming a range of effect sizes rather than a fixed effect size, in which the only variation is assumed to be statistical. An odds ratio (used when studies included in meta-analysis reported outcomes as proportions) or standardized mean difference was calculated as the effect size for each meta-analysis. The results reported for each study were pooled using weighted averages and tested for significance using a Z-statistic. Heterogeneity was investigated using the Q-statistic, and if significant, effects were examined using a one study removed procedure. In each meta-analysis, a funnel plot was constructed, and a Kendall's tau statistic was calculated to assess for publication bias. A classic fail-safe N was also calculated as an indication of how many studies showing no effect would be required to nullify the findings. A quality assessment to examine potential for bias was conducted using the widely used Jadad scale as modified for the purposes of this study.[19,23] Lower scores indicated more potential for bias. To determine whether bias might have affected the findings, bias scores and effect sizes for each meta-analysis were correlated, and a *t* test was conducted to determine if each correlation was significant. The a priori alpha level for finding a significant effect was 0.05.

RESULTS

As displayed in Figure 1, 298 articles were included in this systematic review (included studies are listed in Supplemental Digital Content Appendices B and C at http://links.lww.com/MLR/A102). In total, 224 studies reported therapeutic outcomes, 120 reported humanistic outcomes, and 73 reported safety outcomes; multiple outcome areas were reported in 105 (35.2%) of the 298 included studies. Interrater reliability for the review teams ranged from 0.83 to 0.94 ($P < 0.05$). Summary characteristics of the included studies are presented in Table 1. The majority of studies were conducted in outpatient settings (65.1%). In addition, 144 (48.3%) studies reported Level 1 outcomes (clinical and QoL outcomes). For the RCTs included in the meta-analyses, only 12 of the 81 studies (15%) scored less than 3 on the 5-point modified Jadad scale, indicating the majority of studies were of moderate quality or better. The most frequently reported pharmacists' direct patient care interventions/services where pharmacists had a key role in making or recommending medication adjustments were as follows: medication understanding education ($n = 156$); disease understanding education ($n = 106$); medication or intervention adherence education ($n = 101$); prospective or retrospective drug utilization review ($n = 99$); and chronic disease management ($n = 86$).

Regarding patient characteristics, only 26 studies included pediatric patients (less than 18 years), whereas 218 studies included adults aged 18 to 65 years; and 164 studies included adults older than 65 years (some studies reported multiple age groups, whereas other studies did not report age). In terms of race and ethnicity, White and African-American were the most frequently reported groups, followed by an undefined "Other" category and Hispanic; however, race and ethnicity were not reported in the majority of studies. Patient health care coverage was not reported in 55% ($n = 164$) of studies. The most frequently reported disease states in order were hypertension, dyslipidemia, diabetes, anticoagulation, asthma/chronic obstructive pulmonary dis-

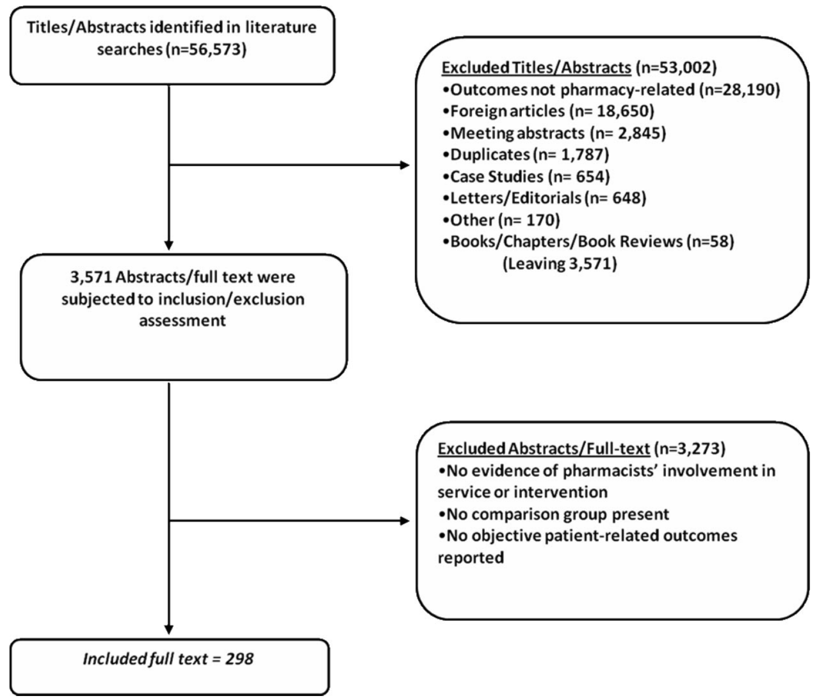

FIGURE 1. Systematic review inclusion/exclusion flowchart.

ease, infection, and psychiatric conditions. The summary of results of pharmacists' effects on direct patient care outcomes (ie, therapeutic, safety, and humanistic) is presented in Table 2, and further discussed later.

Therapeutic Outcomes

Of the 224 studies reporting therapeutic outcomes, largely favorable results were found, meaning a significant improvement in a given therapeutic outcome occurred as a result of pharmacists' direct patient care interventions/services in comparison to an alternative form of care, usually conventional care. More specifically, favorable results were found in 51.4% (18 of 35 studies reporting hospitalization/readmission) to 100% (all 7 studies reporting eye exams) of studies reporting various therapeutic outcomes, as displayed in Table 2. As the most frequently reported therapeutic outcomes, the following were selected to undergo meta-analyses, and it was found that pharmacists' interventions/services significantly improved these outcomes (Fig. 2).

- Hemoglobin A1c: standardized mean difference was 0.6, $P = 0.005$. The mean difference between the pharmacist intervention group and the comparison group in hemoglobin A1c reduction was −1.8% (SD = 0.5; 95% CI = −2.7 to −0.9).
- Low density lipoprotein (LDL) cholesterol: standardized mean difference was 0.3, $P = 0.01$. The mean difference between the pharmacist intervention group and the comparison group in LDL cholesterol reduction was −6.3 mg/dL (SD = 0.12; 95% CI = −6.5 to −6.0).
- Blood pressure (BP): standardized mean difference for diastolic BP was 0.3, $P = 0.001$, and standardized mean difference for systolic BP was 0.5, $P < 0.001$. The mean difference between the pharmacist intervention group and the comparison group in systolic BP reduction was −7.8 mm Hg (SD = 1.5; 95% CI = −9.7 to −5.8). The mean difference between the groups in diastolic BP reduction was −2.9 mm Hg (SD = 0.7; 95% CI = −3.8 to −2.0).

The funnel plot for the diastolic BP analysis indicated that there might be publication bias; however, Kendall's tau ($P = 0.09$) indicated the possibility of bias was low. The funnel plot for the systolic BP analysis did not suggest bias was likely, and Kendall's tau supported this interpretation ($P = 0.62$). The classic fail-safe N was 120 for the diastolic BP analysis and 472 for the systolic BP analysis, indicating that 120 studies and 472 studies, respectively, with no effect would be required to nullify the observed effect. The classic fail-safe N was 31 for LDL cholesterol and 41 for hemoglobin A1c. Funnel plots indicated there were not significant publication biases in the LDL cholesterol and hemoglobin A1c meta-analyses, and Kendall's tau was not significant for either analysis ($P = 0.216$ and 0.188, respectively). The quality assessment for the BP studies indicated that methodological bias was unlikely; the Pearson correlation between the size of the effect and the quality score was −0.08 ($P > 0.05$), indicating there was no correlation between quality score and effect. The quality assessments for the LDL cholesterol and hemoglobin A1c studies showed small to moderate correlations (0.39 and 0.67, respectively) between study quality and effect; however, neither was statistically significant ($P = 0.338$ and 0.146, respectively). The heterogeneity statistics were 59 ($P < 0.001$) for the diastolic BP analysis, 80 ($P < 0.001$) for systolic BP, 14.2 ($P = 0.048$) for LDL cholesterol, and 20.3 ($P = 0.001$) for hemoglobin A1c, indicating that there was variation in the effects of pharmacists' interventions/services. Examination of single study in-

TABLE 1. Summary of Characteristics of Included Studies (n = 298)

Study Characteristics	n (%)
Hierarchy of study outcomes*	
Level 1	144 (48.3%)
Level 2	98 (32.9%)
Level 3	47 (15.8%)
Level 4	9 (3%)
Study setting†	
Inpatient/institutional	88 (29.5%)
Outpatient/ambulatory care/retail/community	194 (65.1%)
Emergency department/urgent care	4 (1.3%)
Home	13 (4.4%)
Other	14 (4.7%)
Pharmacists' interventions‡	
Behavioral	1 (0.3%)
Educational	40 (13.4%)
Technical	75 (25.2%)
Combination/multimodal	182 (61.1%)
Patients' health care coverage§	
Medicaid	19 (6.4%)
Medicare	16 (5.4%)
VA/DoD	41 (13.8%)
Managed care/HMO	28 (9.4%)
Private	19 (6.4%)
Self-insured	8 (2.7%)
Uninsured	17 (5.7%)
Not reported	164 (55%)

*Hierarchy of Outcomes levels defined as follows: (*a*) Level 1, Clinical and Quality of Life (QoL) outcomes (eg, morbidity, mortality, adverse events, QoL); (*b*) Level 2, Surrogate outcomes (eg, blood glucose, blood pressure, cholesterol levels); (*c*) Level 3, other measureable variables with an indirect or unestablished connection to the target outcome (eg, medication or disease state knowledge); and (*d*) Level 4, other relevant variables, but not direct outcomes (eg, patient satisfaction, potential adverse events).[21,22]

†Please note, more than one study setting was reported in a small number of studies.

‡Pharmacist intervention categories defined as follows: (1) educational—-focuses on teaching and providing knowledge related to the patient's medical condition and medication regimen; (2) behavioral—-attempts to modify a patient's behaviors through the use of cues, reminders, or reinforcement; (3) technical—-addresses the medication regimen; strategies include therapeutic change or interchange, simplifying the dosing regimen or schedule, and the use of tools such as pillboxes; and (4) combination/multimodal—-uses strategies from more than one of the above 3 categories (technical, educational, behavioral).

§Please note, more than one health care coverage provider was reported in a number of studies.

DoD indicates Department of Defense; HMO, health maintenance organization; VA, Veteran's Administration.

fluence in each therapeutic meta-analysis, as described by Koshman et al[7] and Tobias,[24] found that removal of any one study did not change the significance of the *P* value (in other words, any one study could be removed and each meta-analysis would remain statistically significant).

Safety Outcomes

Favorable results were found in 60% (9 of 15 studies reporting adverse drug reactions) to 81.8% (9 of 11 studies reporting medication errors) of studies reporting various safety outcomes (Table 2). Adverse drug events were submitted for meta-analysis as it was the only safety outcome reported in more than 4 RCTs with sufficient data for meta-analysis (Fig. 3). There was a significant effect as the odds

TABLE 2. Summary of Outcomes and Results

Outcomes and Results	n (%)
Therapeutic outcomes	
Blood pressure	n = 59
Favorable results	50/59 (84.7%)
Not favorable results	0/59
Mixed results	2/59 (3.4%)
No effect	7/59 (11.9%)
Cholesterol*	n = 54
Favorable results	44/54 (81.5%)
Not favorable results	0/54
Mixed results*	4/54 (7.4%)
No effect	6/54 (11.1%)
Hemoglobin A1c	n = 36
Favorable results	32/36 (88.9%)
Not favorable results	0/36
Mixed results	2/36 (5.5%)
No effect	2/36 (5.5%)
Hospitalization/readmission	n = 35
Favorable results	18/35 (51.4%)
Not favorable results	1/35 (2.9%)
Mixed results	1/35 (2.9%)
No effect	15/35 (42.9%)
Length of hospital stay	n = 32
Favorable results	19/32 (59.4%)
Not favorable results	0/32
Mixed results	3/32 (9.4%)
No effect	10/32 (31.3%)
Emergency department visit	n = 25
Favorable results	13/25 (52%)
Not favorable results	0/25
Mixed results	0/25
No effect	12/25 (48%)
INR/PT/aPTT†	n = 20
Favorable results	17/20 (85%)
Not favorable results	0/20
Mixed results	0/20
No effect	3/20 (15%)
Mortality‡	n = 18
Favorable results	13/18 (72.2%)
Not favorable results	0/18
Mixed results	1/18 (5.6%)
No effect	4/18 (22.2%)
Body mass index/weight	n = 16
Favorable results	10/16 (62.5%)
Not favorable results	0/16
Mixed results	1/16 (6.3%)
No effect	5/16 (31.3%)
Blood glucose§	n = 11
Favorable results	9/11 (81.8%)
Not favorable results	0/11
Mixed results	1/11 (9.1%)
No effect	1/11 (9.1%)
Appropriate medication use¶	n = 9
Favorable results	6/9 (66.7%)
Not favorable results	0/9

(*Continued*)

TABLE 2. (*Continued*)

Outcomes and Results	n (%)
Mixed results	2/9 (22.2%)
No effect	1/9 (11.1%)
Lab monitoring/screening	n = 9
Favorable results	8/9 (88.9%)
Not favorable results	0/9
Mixed results	0/9
No effect	1/9 (11.1%)
Appropriate medication dose	n = 8
Favorable results	7/8 (87.5%)
Not favorable results	0/8
Mixed results	0/8
No effect	1/8 (12.5%)
Aspirin use‖	n = 8
Favorable results	7/8 (87.5%)
Not favorable results	0/8
Mixed results	0/8
No effect	1/8 (12.5%)
Primary care/urgent care visit**	n = 14
Favorable results	10/14 (71.4%)
Not favorable results	0/14
Mixed results	0/14
No effect	4/14 (28.6%)
Asthma measures††	n = 7
Favorable results	6/7 (85.7%)
Not favorable results	0/7
Mixed results	0/7
No effect	1/7 (14.3%)
Eye exam‡‡	n = 7
Favorable results	7/7 (100%)
Not favorable results	0/7
Mixed results	0/7
No effect	0/7
Safety outcomes	
Adverse drug event	n = 28
Favorable results	22/28 (78.6%)
Not favorable results	0/28
Mixed results	0/28
No effect	5/28 (17.9%)
Unclear	1/28 (3.6%)
Adverse drug reactions	n = 15
Favorable results	9/15 (60%)
Not favorable results	0/15
Mixed results	2/15 (13.3%)
No effect	3/15 (20%)
Unclear	1/15 (6.7%)
Medication errors	n = 11
Favorable results	9/11 (81.8%)
Not favorable results	0/11
Mixed results	1/11 (9.1%)
No effect	1/11 (9.1%)
Other safety outcomes§§	n = 46
Favorable results	34/46 (73.9%)
Not favorable results	2/46 (4.3%)
Mixed results	4/46 (8.7%)
No effect	6/46 (13%)

TABLE 2. (*Continued*)

Outcomes and Results	n (%)
Humanistic outcomes	
Patient adherence	n = 54
Favorable results	26/54 (48.1%)
Not favorable results	0/54
Mixed results	11/54 (20.4%)
No effect	15/54 (27.8%)
Unclear	2/54 (3.7%)
Patient knowledge	n = 35
Favorable results	20/35 (57.1%)
Not favorable results	0/35
Mixed results	9/35 (25.7%)
No effect	5/35 (14.3%)
Unclear	1/35 (2.9%)
Patient satisfaction	n = 41
Favorable results	20/41 (48.8%)
Not favorable results	1/41 (2.4%)
Mixed results	10/41 (24.4%)
No effect	10/41 (24.4%)
Quality of life	n = 31
Favorable results	4/31 (12.9%)
Not favorable results	0/31
Mixed results	12/31 (38.7%)
No effect	14/31 (45.2%)
Unclear	1/31 (3.2%)

*Cholesterol outcomes include total cholesterol, low density lipoprotein cholesterol (LDL-C), LDL-C at goal, percent at target LDL-C, LDL-C <100 mg/dL, triglycerides, high density lipoprotein cholesterol, etc. Two of the 4 studies with mixed results reported for cholesterol outcome had favorable outcomes for LDL-C.

†INR = International Normalized Ratio, PT = Prothrombin Time, and aPTT = Activated Partial Thromboplastin Time, also known as Partial Thromboplastin Time (PTT); outcomes include INR level, mean INR, PT ratio, aPTT value, therapeutic INR, therapeutic PT, etc.

‡Mortality outcomes include mortality rate, death rate, total mortality, etc.

§Blood glucose (BG) outcomes include BG level, morning BG, random BG, fasting BG, etc.

¶Appropriate medication use outcomes include appropriateness of medication regimen, mediation appropriateness index.

‖Aspirin use outcomes include use of aspirin for primary or secondary cardiac protection, aspirin use after myocardial infarction, aspirin use in diabetic patients, etc.

**Primary care visit or visit with a medical provider for urgent issues (not emergency department visit), not as a scheduled follow-up.

††Asthma measures include peak flow rate, asthma symptom score, etc.

‡‡Most of the eye exam outcomes were looking at annual diabetes eye screening visits.

§§Includes primarily: hospitalizations related to untoward medication event, drug related problems/interactions, emergency room visits, and medication/prescribing appropriateness; 46 other safety outcomes were reported in 31 studies (9 of these studies reporting more than one other safety outcome).

ratio was 0.53, which represents a significant reduction in the odds of adverse drug events of 47% ($P = 0.01$) in the pharmacist-provided care group versus the comparison group. The heterogeneity statistic was not significant (6.9, $P = 0.143$). A funnel plot indicated there was no publication bias, and Kendall's tau was not significant ($P = 0.14$). The studies scored 4 or 5 on the quality assessment, and the correlation between quality score and effect (0.59) was not significant ($P = 0.306$).

Humanistic Outcomes

As noted in Table 2, favorable results were found in 12.9% (4 of 31 studies reporting QoL) to 57.1% (20 of 35

Outcome	Type	Study	Jadad Score[a]	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hemoglobin A1c		Choe, 2005	5	-0.73	0.23	0.05	-1.18	-0.28	-3.17	0.00
		Rothman, 2005	5	-0.28	0.14	0.02	-0.57	-0.00	-1.96	0.05
		Jaber, 1996	4	-0.76	0.33	0.11	-1.41	-0.10	-2.26	0.02
		Scott, 2006	4	-1.24	0.32	0.10	-1.86	-0.62	-3.89	0.00
		Odegard, 2005	4	0.12	0.23	0.05	-0.33	0.57	0.51	0.61
		Taylor, 2003	3	-2.22	0.84	0.71	-3.88	-0.57	-2.64	0.01
		All studies		-0.63	0.22	0.05	-1.07	-0.19	-2.82	0.00
LDL Cholesterol		Lee, 2006	5	-0.04	0.18	0.03	-0.40	0.32	-0.22	0.83
		Faulkner, 2000	4	-0.46	0.37	0.14	-1.18	0.27	-1.24	0.22
		Ellis, 2000	4	-0.22	0.13	0.02	-0.47	0.03	-1.70	0.09
		Scott, 2006	4	-0.45	0.18	0.03	-0.79	-0.10	-2.52	0.01
		Nola, 2000	3	0.02	0.28	0.08	-0.53	0.57	0.07	0.94
		Jaber, 1996	3	-0.31	0.32	0.11	-0.94	0.33	-0.94	0.35
		Taylor, 2003	3	-2.16	0.64	0.40	-3.41	-0.92	-3.40	0.00
		Bogden, 1997	3	-0.56	0.26	0.07	-1.06	-0.06	-2.18	0.03
		All studies		-0.33	0.12	0.01	-0.57	-0.09	-2.73	0.01
Blood Pressure	Group by Type									
	Diastolic	Lee, 2006	5	-0.11	0.17	0.03	-0.45	0.23	-0.63	0.53
	Diastolic	Green, 2008	5	-0.45	0.09	0.01	-0.63	-0.27	-4.85	0.00
	Diastolic	Jaber, 1996	4	-0.64	0.33	0.11	-1.28	0.01	-1.92	0.05
	Diastolic	Schneider, 2008	4	-0.48	0.22	0.05	-0.91	-0.04	-2.15	0.03
	Diastolic	Mehos, 2000	4	-0.57	0.41	0.17	-1.37	0.23	-1.39	0.16
	Diastolic	Solomon, 1998	3	-0.28	0.17	0.03	-0.62	0.06	-1.62	0.11
	Diastolic	Okamoto, 2001	3	-0.32	0.11	0.01	-0.54	-0.10	-2.87	0.00
	Diastolic	Vivian, 2002	3	-0.26	0.28	0.08	-0.80	0.28	-0.95	0.34
	Diastolic	Chisholm,2002	3	-0.91	0.44	0.19	-1.78	-0.05	-2.06	0.04
	Diastolic	Hennessy, 2006	3	0.00	0.02	0.00	-0.05	0.05	0.00	1.00
	Diastolic	Taylor, 2003	3	-1.85	0.47	0.22	-2.77	-0.94	-3.97	0.00
	Diastolic	Park, 1996	2	-0.05	0.29	0.08	-0.61	0.51	-0.18	0.86
	Diastolic	Hawkins, 1979	2	0.00	0.08	0.01	-0.16	0.16	0.00	1.00
	Diastolic	All studies		-0.31	0.09	0.01	-0.50	-0.13	-3.41	0.00
	Systolic	Lee, 2006	5	-0.50	0.18	0.03	-0.84	-0.16	-2.85	0.00
	Systolic	Green, 2008	5	-0.62	0.09	0.01	-0.81	-0.44	-6.70	0.00
	Systolic	Mehos, 2000	4	-0.57	0.41	0.17	-1.37	0.23	-1.39	0.16
	Systolic	Scott, 2006	4	-0.38	0.17	0.03	-0.70	-0.05	-2.28	0.02
	Systolic	Jaber, 1996	4	-0.32	0.32	0.11	-0.96	0.32	-0.99	0.32
	Systolic	Schneider, 2008	4	-0.28	0.22	0.05	-0.71	0.15	-1.28	0.20
	Systolic	Okamoto, 2001	3	-0.39	0.11	0.01	-0.61	-0.18	-3.54	0.00
	Systolic	Vivian, 2002	3	-1.02	0.29	0.09	-1.59	-0.44	-3.48	0.00
	Systolic	Chisholm, 2002	3	-2.06	0.52	0.27	-3.07	-1.04	-3.96	0.00
	Systolic	Hennessy, 2006	3	-0.12	0.02	0.00	-0.16	-0.07	-4.99	0.00
	Systolic	Solomon, 1998	3	-0.35	0.17	0.03	-0.70	-0.01	-2.01	0.04
	Systolic	Taylor, 2003	3	-1.85	0.47	0.22	-2.77	-0.94	-3.97	0.00
	Systolic	Park, 1996	2	-0.32	0.29	0.08	-0.89	0.24	-1.13	0.26
	Systolic	Hawkins, 1979	2	-0.38	0.08	0.01	-0.53	-0.22	-4.64	0.00
	Systolic	All studies		-0.49	0.09	0.01	-0.66	-0.32	-5.53	0.00
	Overall	All studies		-0.40	0.09	0.01	-0.58	-0.23	-4.60	0.00
Medication Adherence		Rathbun, 2005	5	-0.63	0.36	0.13	-1.33	0.07	-1.77	0.08
		Lee, 2006	5	-2.09	0.20	0.04	-2.48	-1.70	-10.59	0.00
		Schneider, 2008	4	-0.58	0.22	0.05	-1.02	-0.15	-2.62	0.01
		Finley, 2003	4	-0.44	0.25	0.06	-0.93	0.04	-1.80	0.07
		Faulkner, 2000	4	0.00	0.59	0.35	-1.16	1.16	0.00	1.00
		Capoccia, 2004	4	-0.02	0.26	0.07	-0.53	0.49	-0.08	0.93
		Murray, 2007	4	-0.42	0.12	0.01	-0.65	-0.20	-3.63	0.00
		Solomon, 1998	3	-1.01	0.18	0.03	-1.37	-0.64	-5.46	0.00
		Simkins (1), 1986	3	-0.13	0.14	0.02	-0.40	0.14	-0.93	0.35
		Simkins (2), 1986	3	-0.13	0.19	0.03	-0.49	0.24	-0.68	0.49
		Lipton & Bird, 1994	3	-0.51	0.14	0.02	-0.79	-0.24	-3.63	0.00
		Garnett, 1981	3	-0.40	0.33	0.11	-1.06	0.25	-1.21	0.23
		Hawkins, 1979	2	-0.17	0.19	0.04	-0.55	0.20	-0.90	0.37
		Chisholm, 2001	1	-1.65	0.47	0.22	-2.58	-0.72	-3.49	0.00
		All studies		-0.58	0.15	0.02	-0.88	-0.28	-3.78	0.00
Patient Knowledge		Voirol, 2004	5	-0.21	0.33	0.11	-0.85	0.43	-0.65	0.52
		Woroniecki, 1982	4	-1.61	0.28	0.08	-2.16	-1.06	-5.70	0.00
		Gourley, 1998	3	-0.36	0.18	0.03	-0.71	-0.02	-2.06	0.04
		Soflin, 1977	2	-1.61	0.59	0.35	-2.77	-0.44	-2.70	0.01
		Skoutakis, 1978	2	-2.09	0.51	0.26	-3.09	-1.10	-4.12	0.00
		Self, 1983	1	-1.41	0.51	0.26	-2.42	-0.41	-2.75	0.01
		All studies		-1.14	0.33	0.11	-1.79	-0.48	-3.41	0.00
Quality of Life – General Health Dimension		Green, 2008	5	-0.00	0.09	0.01	-0.18	0.17	-0.05	0.96
		Malone, 2001	5	-0.15	0.06	0.00	-0.27	-0.03	-2.48	0.01
		Gourley, 1998	3	-0.21	0.20	0.04	-0.61	0.19	-1.04	0.30
		Okamoto, 2001	3	-0.19	0.11	0.01	-0.41	0.02	-1.74	0.08
		Taylor, 2003	3	-0.39	0.24	0.06	-0.87	0.09	-1.60	0.11
		All studies		-0.13	0.04	0.00	-0.22	-0.05	-3.00	0.00

Statistics for each study

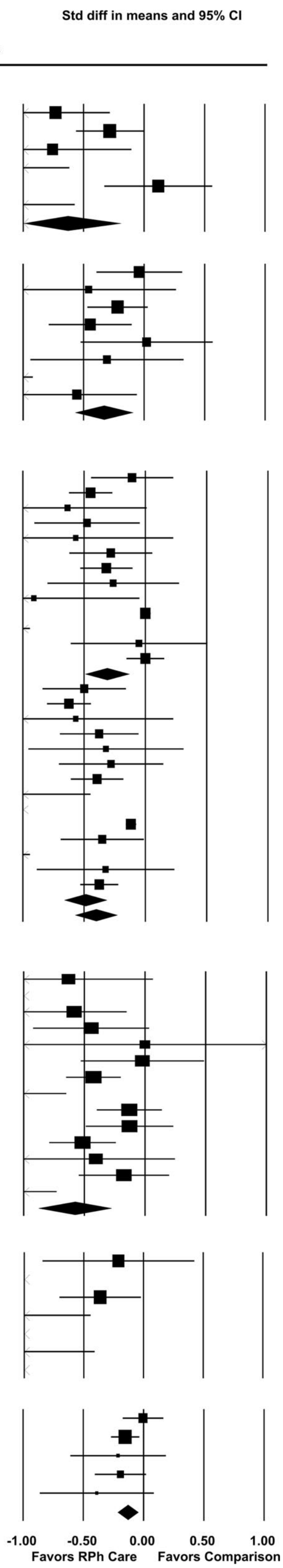

FIGURE 2. Forest Plots, and Therapeutic and Humanistic Outcomes (Pharmacist Intervention/Service vs. Comparison). This figure displays the effects of pharmacist-provided interventions/services versus comparison on selected therapeutic and humanistic outcomes. Six studies were included in the hemoglobin A1c meta-analysis (sample size = 550). Eight studies were included in the LDL cholesterol meta-analysis (sample size = 745). Fourteen studies (note, one study has usable data only

Study	Jadad Score[a]	Odds ratio	Lower limit	Upper limit	Z - Value	p - Value
		Statistics for each study				
Schnipper etal, 2006	5	0.12	0.01	1.00	- 1.96	0.05
Hanlon etal, 1996	4	0.66	0.35	1.24	- 1.30	0.20
Jameson, 2001	4	0.59	0.34	1.03	- 1.86	0.06
Murray, 2007	4	0.67	0.41	1.07	- 1.67	0.09
Powers, 1983	4	0.09	0.02	0.53	- 2.68	0.01
All studies		0.53	0.33	0.83	- 2.73	0.01

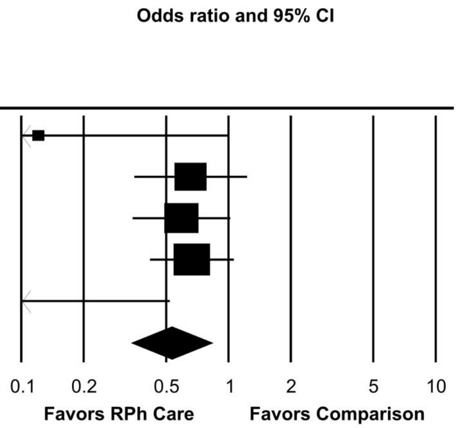

FIGURE 3. Forest Plot, Adverse Drug Events (Pharmacist Intervention/Service vs. Comparison). Five studies were included in the adverse drug events meta-analysis (sample size = 937). The pooled effect of the meta-analysis, represented by the diamond symbol in the forest plot, favors pharmacist-provided care. [a]Jadad score based on modified Jadad scale. RPh indicates pharmacist.

studies reporting patient knowledge) of studies reporting humanistic outcomes (patient adherence, patient satisfaction, patient knowledge, and QoL). Six humanistic outcomes were selected for meta-analyses: medication adherence, patient satisfaction, patient knowledge, QoL-general health, QoL-physical functioning, and QoL-mental health (as QoL has several dimensions, these 3 dimensions were considered most appropriate to an investigation of pharmacists' effects). Significant results favoring pharmacists' interventions were found in 3 (Fig. 2) of the 6 meta-analyses (1): medication adherence (standardized mean difference, 0.6, $P = 0.001$); (2) patient knowledge (standardized mean difference, 1.1, $P = 0.001$); and (3) QoL-general health (standardized mean difference, 0.1, $P = 0.003$). The remaining meta-analyses indicated no differences between the groups ($P > 0.05$). The heterogeneity statistic was significant in the adherence and knowledge (97.1 and 27.4, respectively; $P < 0.001$) meta-analyses, but not in the QoL-general health meta-analysis ($P > 0.05$). Examination of single study influence in the adherence and knowledge meta-analyses found that removal of any one study did not affect significance. The classic fail-safe N was 339 for medication adherence, 79 for patient knowledge, and 8 for QoL-general health. Funnel plots and Kendall's tau ($P = 0.352$ and 0.131, respectively) for the adherence and knowledge meta-analyses did not show evidence of publication bias. The funnel plot for the QoL-general health analysis indicated there might be some publication bias; however, Kendall's tau was not significant ($P = 0.327$). The Pearson correlations of the quality assessments of the 3 meta-analyses were 0.01 for medication adherence, 0.59 for patient knowledge, and 0.74 for QoL-general health; none were statistically significant ($P \geq 0.152$).

DISCUSSION

Medication distribution is perhaps the most well-known role of a pharmacist, and remains an essential part of the conventional functions of a pharmacist. Evidence documented in this systematic review demonstrates the effects of pharmacist-provided direct patient care on various health care outcomes, which extend beyond medication distribution. Previous research suggests that pharmacist-provided care may be a cost-effective alternative to traditional care.[25–29] For example, Boyko et al found that inpatients treated by a health care team that included a pharmacist had significantly shorter length of stay and lower pharmacy and total hospital costs compared with inpatients whose health care teams did not include a pharmacist.[28] Thus, because of their education and specialized training, pharmacists offer clinical expertise, unique insights, and beneficial recommendations regarding medication use/monitoring and patient management that result in improved therapeutic, safety, and humanistic outcomes, and may contribute to more cost-effective health care.

Among therapeutic outcomes, pharmacists' direct patient care interventions/services demonstrate a favorable effect on outcomes such as International Normalized Ratio/prothrombin time/activated partial thromboplastin time, body mass index/weight, and appropriate medication dose and monitoring. Other therapeutic outcomes such as mortality, hospitalization/readmission, inpatient length of stay, and

FIGURE 2. (*Continued*) for the systolic blood pressure analysis) were included in the blood pressure meta-analysis (sample size: systolic = 9357; diastolic = 9208). Thirteen studies (note, one study was included twice as there were 2 treatment groups in the study) were included in the medication adherence meta-analysis (sample size = 1720). Six studies were included in the patient knowledge meta-analysis (sample size = 429). Five studies were included in the quality of life-general health dimension meta-analysis (sample size = 2070). The pooled effect of each meta-analysis, represented by the diamond symbol in each forest plot, favors pharmacist-provided care. [a]Jadad score based on modified Jadad scale. RPh indicates pharmacist; std diff, standardized difference.

emergency department visits also benefit greatly from pharmacist-provided services. For example, a study comparing interdisciplinary inpatient care teams with or without clinical pharmacists found that patients treated by teams with pharmacists experienced shorter hospitals stays and required fewer returns to the intensive care unit.[26] Previous systematic reviews have documented similar favorable findings such as decreased hospital readmissions, length of hospital stays, and mortality as a result of pharmacist interventions.[2,11,22,30] For example, Ponniah et al found that 6 of 7 studies examining postdischarge pharmacy services among patients with heart failure reported positive therapeutic outcomes including reduced unplanned hospital readmissions and death rates.[11] The cumulative evidence provided by this review and earlier studies regarding pharmacists' effects on the aforementioned therapeutic outcomes is particularly important given the rising costs of health care in the United States, where spending for hospital care alone accounted for 31% of health care expenditures in 2007.[31]

In addition, prior systematic reviews have found that pharmacist interventions result in decreased blood pressure, hemoglobin A1c, cholesterol, and risk factors for coronary heart disease.[8,9,12–14,22,32] Likewise, the hemoglobin A1c, LDL cholesterol, and BP meta-analyses of this study clearly demonstrate that pharmacist-provided direct patient care can substantially improve these clinical markers. These findings suggest that pharmacists' interventions such as medication education and disease management may greatly improve surrogate endpoints—and controlling BP, LDL cholesterol, and hemoglobin A1c have been shown to reduce adverse sequelae such as myocardial infarction, stroke, amputations, and other comorbidities associated with hypertension, dyslipidemia, and diabetes. For example, long-term follow-up of the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study suggested that treatment to hemoglobin A1c targets below or approximately 7% was associated with long-term reduction in risk of macrovascular disease.[33,34] Furthermore, each 1% reduction in hemoglobin A1c was associated with reductions in risk of 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications.[34] The relationship between controlled BP and LDL-cholesterol and clinical outcomes has been established through both epidemiological and patient-oriented clinical trials. For example, each mg/dL reduction in LDL-cholesterol has been correlated with an approximately 1% relative risk reduction for cardiovascular events, whereas a 3-mm BP reduction has been associated with a 5% reduction in coronary-related deaths and an 8% reduction in stroke-related deaths.[35–40] Given the possible adverse health outcomes combined with the high costs ($152 billion–$312 billion) and prevalence (8%–29%) of hypertension, dyslipidemia, and diabetes in the United States,[41–46] pharmacists' direct patient care services can benefit chronic disease management and possibly reduce costs of care.

As the prevalence of chronic disease increases in the United States, undoubtedly medication use and demand for pharmacists' expertise will also increase. According to a 2006 report, 82% of adults and 56% of children take at least one medication in any given week.[47] Since 2000, the percentage of adults taking at least 5 medications (both prescription and nonprescription) increased from 23% to 29%, with prescription use of 5 or more drugs doubling (from 6% to 12%).[47] This increase in medication use, particularly the rise in multidrug regimens, may contribute to the notable incidence of medication errors, adverse drug events, and other medication safety issues among patients. The IOM focused the nation's health care system on patient safety related to medication use, estimating that 1.5 million preventable adverse drug events occur annually because of medication errors, at a cost of billions of dollars.[48] Furthermore, the IOM noted that pharmacists can play a substantive role in the reduction of adverse drug events and other medication-related threats to patient safety, a conclusion supported by the safety results of this study.[4,48] Our findings suggest that pharmacists' interventions/services have a largely favorable effect on safety outcomes in the following categories: adverse drug events, adverse drug reactions, medication errors, and other outcomes including hospitalizations related to untoward medication events. Similarly, previous systematic reviews have also demonstrated mostly favorable findings regarding the impact of pharmacists' interventions/services on safety outcomes.[2,8,32,49] Kaboli et al, for example, found that pharmacists reduced the incidence of both preventable and total adverse drug events in 5 of 7 studies in a systematic review of clinical pharmacists in inpatient settings.[2]

The findings pertaining to the humanistic outcome area are somewhat favorable, which is consistent with previous systematic reviews of pharmacists' effects on humanistic outcomes.[2,8–10,14–16,22,32,49] However, the humanistic findings have more variability than the therapeutic and safety areas. In the case of patient adherence, satisfaction, and knowledge, findings favoring pharmacists' interventions/services were reported in 48% to 57% of studies in each category (Table 2), with the highest percentage of favorable results found in enhancing patients' knowledge about medication and disease states. In studies reporting QoL as an outcome, no effect and mixed results accounted for more than 80% of studies, suggesting that pharmacists' interventions/services may have little overall statistically significant influence on QoL. Unlike therapeutic or safety outcomes that rely on objective assessment and measurement, humanistic outcomes are generally based on the perspective and perceptions of patients. As noted by Coons, "Physiologic measures may change without improving functioning and well-being [which are humanistic outcomes]. Likewise, patients may feel and function better without measurable change in physiologic values" (p. 16).[50] Another factor that may limit the effect of pharmacists' interventions on humanistic outcomes, particularly QoL, is time—the duration of interventions/services may not be long enough to facilitate significant changes in outcome measures. Thus, although our findings suggest that pharmacists' services have generally favorable effects on humanistic outcomes, particularly among those outcomes that are arguably most directly related to the work of pharmacists (ie, patient adherence and patient knowledge), the evidence is not overwhelming.

There are some limitations to this systematic review and meta-analyses. As with any systematic review and meta-analyses, the possibility of publication bias must be taken into account. Publication bias may occur under the following circumstances: (1) all studies relevant to a particular inquiry are not published; and (2) studies reporting favorable results are more likely to be published than those reporting negative results. Thus, even as the 298 included articles are representative of the extent and scope of pharmacist services/interventions (ie, pharmacists' effects as team members in direct patient care) in published studies, the review may not represent pharmacists' interventions/services in unpublished studies. It was also noted that the majority of studies did not report power and sample size analyses, and therefore, studies with no effect results may not have been powered sufficiently to detect statistically significant differences. There were differences in pharmacist activities among studies, making it difficult to precisely determine which intervention(s) provides optimal outcomes; likewise, unintentional cointerventions may have occurred, making it difficult to determine their presence and effects. Heterogeneity was found in the hemoglobin A1c, LDL cholesterol, BP, medication adherence, and patient knowledge meta-analyses and may be attributable to factors such as differences in potency of various interventions or the incomplete adoption of interventions within studies. However, in each meta-analysis, assessment of single study effect revealed that removal of any one study did not nullify the statistical significance of the *P* value.

Future studies addressing the effects of pharmacist-provided direct patient care should comprehensively integrate assessment of long-term, level 1 outcomes such as morbidity and mortality. Although surrogate markers (eg, hemoglobin A1c) are important, they should be used in conjunction with more definitive indicators of health and well-being within a patient population. Moreover, the types of interventions/services provided by pharmacists varied widely across the studies included in this systematic review. As a strategy to build and enhance best practice standards, future studies should identify and replicate those interventions/services that may be most effective. For example, future studies should examine the efficacy of the following recommendations made by the IOM to improve medication safety[4,48]:

- Pharmacists should be available on nursing units and on rounds to improve access to medication information.
- Health care settings, particularly inpatient, should ensure pharmaceutical decision support is available (at all times, if possible).
- Pharmacists should be involved in medication management in nursing homes and ambulatory care settings.
- Increase consumer awareness of the right to pharmacist counseling on medications.
- Implement a team-based (including pharmacist) approach to medication reconciliation.
- Generally increase availability of and access to medication management services provided by pharmacists.
- Pharmacists should serve as active participants in the medication use process.

Given the shortages noted in the provision of primary care (eg, lack of physicians), pharmacists may help fill the gap as primary care providers (for example, operating under mechanisms like collaborative practice agreements), particularly in high-need areas such as rural communities.[1] Therefore, future studies are needed to further examine the usefulness of employing pharmacists as primary care providers. As noted previously, health care costs have risen dramatically in recent years, and pharmacist-provided care may prove a viable option to reduce health care costs while providing high-quality care. Thus, future studies of pharmacist-provided direct patient care should include economic assessments.

The current study spans decades of literature and is the most comprehensive and inclusive systematic review to date examining the effects of pharmacist-provided direct patient care. Our findings provide compelling evidence concerning pharmacists' favorable effects on direct patient care and supports pharmacists as key members of the health care team. In particular, the results support the beneficial impact of pharmacist-provided care in the areas of therapeutic (across various outcomes such as hospitalizations, mortality, emergency department visits, and surrogate clinical markers), safety (eg, adverse drug events, adverse drug reactions), and, to some degree, humanistic outcomes. This seminal collective work may be used to promote stakeholders' understanding, recognition, and use of pharmacists' professional services, thus facilitating the increased utilization of pharmacists as members of the health care team and as direct patient care providers.

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